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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,308	10/24/2003	Frank Grosveld	CARP0015-100	1498

34132 7590 06/01/2007  
COZEN O'CONNOR, P.C.  
1900 MARKET STREET  
PHILADELPHIA, PA 19103-3508

EXAMINER
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SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
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1632

MAIL DATE	DELIVERY MODE
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06/01/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Interview Summary</b>	<b>Application No.</b> 10/693,308	<b>Applicant(s)</b> GROSVELD, FRANK	
	<b>Examiner</b> Anoop Singh	<b>Art Unit</b> 1632	

All participants (applicant, applicant's representative, PTO personnel):

- (1) Anoop Singh. (3) Frank Grosveld.  
 (2) Anne Falk. (4) Doreen Trujillo.

Date of Interview: 5/07/07.

Type: a) ☒ Telephonic b) ☐ Video Conference  
 c) ☐ Personal [copy given to: 1) ☐ applicant 2) ☐ applicant's representative]

Exhibit shown or demonstration conducted: d) ☒ Yes e) ☐ No.

If Yes, brief description: Proposed draft amendment from the attorney is attached to the interview summary.

Claim(s) discussed: those of record.

Identification of prior art discussed: Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS); Janssens (Proc Natl Acad Sci U S A. 2006 Oct 10;103(41):15130-5);

Agreement with respect to the claims f) ☐ was reached. g) ☒ was not reached. h) ☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: See Continuation Sheet.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

*Anne Marie Falk*

ANNE-MARIE FALK, PH.D  
 PRIMARY EXAMINER

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: A draft amendment which is attached to this interview summary was received for discussion purposes from the attorney of record. A conference call was made to include the inventor Dr. Grosveld during the interview. Dr. Grosveld discussed the novelty of the invention. It was agreed that proposed draft amendment to independent claim reciting additional step of a regulatory sequence providing expression of VHH heavy chain locus specifically in B cell would overcome the rejection under 35 U.S.C. 112, second paragraph and rejection under 35 U.S.C. 102 by Ledbetter et al (WO 99/42077, dated 08/26/1999, IDS). Applicants noted that specification as filed fully enables the breadth of the claims. Applicant argued that cell specific transgene expression in transgenic mammals was an established technology as of the priority date of the present invention-LCR elements were known to provide integration site independent, tissue specific expression of the incorporated transgene in mammalian genomes. Applicants also indicated support of enablement in a recently published paper (PNAS, 2006, vol. 103, no. 41, 15130-15135) showing Applicants have generated both IgG and IgM heavy chain only antibodies in mice following the disclosure of the specification as filed. In response, Applicants were advised to indicate enabling support in the specification and any post filing art to show how claims are enabled to the full breadth. Further, it was also advised that if applicants rely on post filing art for the enabling support then support for such disclosure should be indicated in the specification. Examiner also indicated that he was aware of relevant art that recognizes species-specific differences in the expression of various transgenes and inefficiency of pronuclear microinjection transgenic techniques and the unpredictability of transgene expression when applied to generating transgenic nonhuman animal. Examiner maintained that it is generally known in the art that random integration of transgenes results in a concatameric array of multiple copies, whereas single copy integrations are unusual. Applicants indicated that they will consider submitting arguments to and/or amendments addressing the rejection of record and would also indicate the enabling support in the specification. .

## Summary of Record of Interview Requirements

### Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

### Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews

#### Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

#### 37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,  
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

#### Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

## Applicant Initiated Interview Request Form

Application No.: 10/693,308 First Named Applicant: Frank Grosveld  
 Examiner: Singh Art Unit: 1632 Status of Application: AFTER FINAL

## Tentative Participants:

(1) Doreen Trujillo (2) Dr. Frank Grosveld  
 (3) \_\_\_\_\_ (4) \_\_\_\_\_

Proposed Date of Interview: 5/7/07 Proposed Time: 2:00 (AM/PM)

## Type of Interview Requested:

(1) ☒ Telephonic (2) ☐ Personal (3) ☐ Video Conference

Exhibit To Be Shown or Demonstrated: ☐ YES

☒ NO

If yes, provide brief description: \_\_\_\_\_

## Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s	Prior Art	Discussed	Agreed	Not Agreed
(1) <u>112, 1st A</u>	<u>1-4, 7-8, 10-11, 33-36</u>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(2) <u>112, 2nd A</u>	<u>same</u>	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(3) <u>102(b)</u>	<u>1-2</u>	<u>Ledbetter</u>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(4) _____	_____	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Continuation Sheet Attached					

## Brief Description of Arguments to be Presented:

claims ds amended are enabled throughout their  
scope, are definite, and are novel

An interview was conducted on the above-identified application on \_\_\_\_\_.

**NOTE:** This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).

This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible.

Applicant/Applicant's Representative Signature \_\_\_\_\_

Examiner/SPE Signature \_\_\_\_\_

Typed/Printed Name of Applicant or Representative \_\_\_\_\_

Registration Number, if applicable \_\_\_\_\_

This collection of information is required by 37 CFR 1.133. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 21 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

**PROPOSED CLAIM AMENDMENTS****(showing support in specification)****Claim 1 (cancelled)**

**Claim 2 (currently amended)** A method ~~according to claim 1~~ for the production of a single heavy chain antibody in a non-human mammal comprising expressing a heterologous VHH heavy chain locus in that mammal specifically in B cells in response to antigen challenge wherein the VHH heavy chain locus comprises:

(a) ~~at least more than~~ [SUPPORT ON PAGE 6, LINES 11-16 AND PAGE 12, LINES 13-19, REGARDING VHH, D, AND J.] one VHH region each comprising one VHH exon, ~~at least more than~~ one D region each comprising one D exon and ~~at least more than~~ one J region each comprising one J exon, wherein the VHH region, the D region and the J region are capable of recombining to form VDJ coding sequence,

(b) a constant heavy chain region comprising at least one constant heavy chain gene, wherein each of said at least one constant heavy chain gene, when expressed, does not express a functional CH1 domain,

(c) a regulatory sequence providing for expression of the VHH heavy chain locus specifically in B cells [SUPPORT ON PAGE 22, LINE 19 THROUGH PAGE 23, LINE 14]and

which locus when expressed leads to the formation of a single heavy chain antibody.

**Claim 3 (cancelled)**

**Claim 4 (currently amended)** A method ~~according to claim 3~~ for the production of a single heavy chain antibody in a non-human mammal comprising expressing a camelised VH heavy chain locus in that mammal specifically in B cells in response to antigen challenge

wherein the camelised VH heavy chain locus comprises:

(a) ~~at least~~ more than one VH region each comprising one VH exon which is mutated such that, when expressed, the resulting single heavy chain antibody is stabilised, at ~~least~~ more than one D region each comprising one D exon and ~~at least~~ more than one J region each comprising one J exon, wherein the VH region, the D region and the J region are capable of recombining to form VDJ coding sequence, and

(b) a constant heavy chain region comprising at least one constant heavy chain gene, wherein each of said at least one constant heavy chain gene, when expressed, does not express a functional CH1 domain,

(c) a regulatory sequence providing for expression of the VHH heavy chain locus specifically in B cells

and which locus when expressed leads to the formation of a single heavy chain antibody.

Claims 5 – 6 (canceled)

Claim 7 (currently amended) A method according to claim ~~1~~ or 2 wherein the VHH single heavy chain locus comprises a camelid VHH, at least one D region of human origin and at least one J region of human origin and a constant region of human origin.

Claim 8 (currently amended) A method according to claim ~~3~~ or 4 wherein the camelised VH heavy chain locus comprises at least one D region of human origin and at least one J region of human origin and a constant region of human origin.

Claim 9 (canceled)

Claim 10 (currently amended) A method according to claim ~~1~~ or ~~3~~ 2 or 4 wherein the constant heavy chain region comprises at least one constant region heavy chain gene which is of

non-camelid origin.

Claim 11 (**original**) A method according to claim 10 wherein at least one constant region heavy chain gene is of human origin.

Claims 12 – 16 (**canceled**)

Claims 17 - 32 (**canceled**)

Claim 33 (**currently amended**) The method of claim ~~1~~ 2 wherein the entire VHH single heavy chain locus is of camelid origin

Claim 34 (**currently amended**) The method of claim ~~3~~ 4 wherein the camelised VH single heavy chain locus is of human origin.

Claim 35 (**currently amended**) The method of claim ~~3~~ 4 wherein the camelised VH single heavy chain locus is of non-human origin.

Claim 36 (**currently amended**) The method of claim ~~3~~ 4 wherein the camelised VH single heavy chain locus is of camelid origin.

Claim 37 (**currently amended**) The method according to claim ~~1~~ ~~or 3~~ 2 or 4 wherein the antibody is a monoclonal antibody, said method further comprising the steps of isolating the spleen from said transgenic animal, fusing said spleen cells with a myeloma to produce hybridoma cells, and isolating said antibody from said hybridoma cells.

Claim 38 (**currently amended**) The method according to claim ~~1~~ ~~or 3~~ 2 or 4 wherein the antibody is a monoclonal antibody, said method further comprising the steps of isolating antibody-producing cells from said transgenic animal, isolating nucleic acid from said cells, utilizing said nucleic acid to prepare a phage display library, selecting phage displaying antigen specific VHH or camelised VH binding domains, and isolating said binding domains.

Claim 39 (**new**) The method according to claim 2 or 4 wherein the non-human



mammal is a rodent.

Claim 40 (new) The method according to claim 2 or 4 wherein the regulatory sequence is a locus control region.